Remarks

Claims 1-8 and 19-24 were examined in this case. Claims 1-8 and 19-24 stand rejected. The present Response amends claim 20. Each of the objections and rejections raised in the Office Action is addressed individually below.

Restriction Requirement

In response to the Applicant's election to traverse filed 10/17/02, the Examiner deemed the Requirement proper and the Requirement has been made final. In support of this decision, the Examiner points to page 3905 of the Nguyen and Southern, where it is stated,

> "for practical applications it will be necessary to incorporate the modified bases in the nucleic acid fragments to be analyzed by an enzymatic reaction, constraining the choice of modified nucleosides to those whose 5'-triphosphates can be used as substrates for DNA polymerases. From the large number of modified nucleosides described in the literature we chose ^{d4Et}C to replace natural deoxycytidine (dC)."

The Examiner relied on this statement to justify limiting review of the present claims to a single polymerase. Applicant respectfully points out that the presently claimed invention is not identifying nucleotides or nucleotide analogues to be used with a given polymerase. Rather, the claims recite methods in which a *set of nucleotide precursors* that, when utilized in an extension reaction on a self-complementary template, will generate a strand that forms intermolecular but not intramolecular base pairs. The inventive principle is not different for different polymerases. The fact that researchers who want to use a particular polymerase focus on selecting nucleotide precursors that can be utilized by that polymerase is neither remarkable nor inventive. In fact, the Nguyen and Southern reference serves to demonstrate Applicant's point that those of ordinary skill in the art, wishing to identify new nucleotide precursors that can be polymerized by a given polymerase, have the skills to do so.

As evidence that the present claims can be searched without limitation to a particular polymerase, Applicant provides the following Summary of searches performed by other patent offices or by the present inventors:

1) A search by inventor Dr. Jeffrey Sampson, a leader in the field of nucleic acid chemistry. Dr. Sampson is an inventor on one issued U.S. patent (6,218,118) and several pending applications in the field. Dr. Sampson's search identified all of the relevant references discussed in detail below; copies of these references are attached in Appendix A. Dr. Sampson's search included the following components:

   a) A citation search[1] of the following three papers; Dr. Sampson was familiar with these papers through his work in the area:

      - Kutyavin et al., "Oligonucleotides Containing 2-Aminoadenine and 2-Thiothymidine act as selectively binding complementary agents" *Biochemistry* 35:11170, 1996
      - Woo et al., "G/C-modified oligodeoxynucleotides with selective complementarity: synthesis and hybridization properties", *Nuc. Acids Res.* 24:2470, 1996
      - Nguyen et al., "Minimising the secondary structure of DNA targets by incorporation of modified deoxynucleosides: implications for nucleic acid analysis by hybridization", *Nuc. Acids Res.* 28:3904, 2000.

   b) A search of the "Web of Science" database (identical to the SciSearch® database) using the following terms:

      - (DNA or RNA or nucleic acid or polynucleotide or oligonucleotide) and (unstructured or destabilize(d))
      - (DNA or RNA or nucleic acid or polynucleotide or oligonucleotide) and (structure or secondary structure) and (reduce(d) or destabilize(d) or stability)

[1] A citation search identifies all *later* publications that include citations to the searched publication.

- minimiz(s)ing and (DNA or RNA or nucleic acid or polynucleotide) and (structure or stability)
- hybridization and reduced stability
- minimizing and hybridization and stability
- duplex and destabilizing
- modified nucleotide and structure
- nucleotide analog and (DNA or RNA or oligonucleotide) structure
- novel and (base paring or base-pairing)
- base-pair(ing) and selective
- base-pair(ing) scheme(s)
- base-pair(ing) system(s)
- base-pair(ing) and (isosteric or isostere)
- selectively and complementary and (DNA or nucleic acid or polynucleotide)
- 2,6-diaminopurine and (DNA or RNA or nucleic acid or polynucleotide)
- 2-aminoadenosine and (DNA or RNA or nucleic acid or polynucleotide)
- 2-amino-2'-deoxyadenosine
- 2-thiothymidine
- 2-thiouridine
- 2'-deoxy-2-thiouridine
- 2-thiocytidine
- 2'-deoxy-2-thiocytidine

c) A search of the front pages (i.e., Title and Abstract) of patents in the MicroPatent data-base (US, PCT and EP) using the following terms (the most comprehensive of the terms used in the literature database search):

- (DNA or RNA or nucleic acid or polynucleotide or nucleotide) and structure and (reduce or minimize or destabilize)

- base pair(ing) and (reduce or minimize or destabilize or stabilize or stability)
- duplex stability
- intramolecular and hybridization
- selective(ly) and binding and complement(ary)
- nucleic acid and complementary and stability
- base pair(ing) and (scheme or non-standard)
- base pair(ing) and system and (DNA or nucleic)
- nucleotide and (incorporation or incorporating)
- modified nucleotide and structure
- 2,6-diaminopurine
- 2-aminoadenosine
- 2-amino-2'-deoxyadenosine
- 2-thiothymidine
- 2-thiouridine
- 2'-deoxy-2-thiouridine
- 2-thiocytidine
- 2'-deoxy-2-thiocytidine

d) A full text patent search in the MicroPatent data-base (US, PCT and EP) using the following terms:

- diaminopurine and 2-thiothymidine
- unstructured nucleic acid (or DNA)
- reduced secondary structure

2) A search made by the European Patent Office. A copy of the European Patent Office's Search Report, which lists ten references and includes an indication that each listed reference is considered to be background art, is attached in Appendix B Copies of the listed references are also included in Appendix B.

The references that are most closely related to the subject matter of the presently claimed invention were all identified in the search by Dr. Sampson. The most relevant references are discussed below:

Mutually-exclusive base pairing

Kutyavin et al. (*Biochemistry* (1996) 35:11170-11176) show that pairs of chemically synthesized oligonucleotides, which possess a complementary sequence and are comprised of the nucleotides G, C, 2-aminoadenosine (D), and 2-thiothymidine (sT), do not form stable intermolecular hybrids with each other but can form stable intermolecular hybrids with their respective complementary oligonucleotide comprised of four natural nucleotides A, G, C, and T. This "selective" base pairing property is due to the inability of D and sT to form stable base pairs (Ds≠T and sT≠D; ≠ indicates reduced levels of base pairing), where D and sT can form a stable base pair with their respective natural complements (D=T, sT=A; = indicates ability to base pair). Kutyavin et al. provide no teaching or suggestion of nucleic acids with complementary sequence elements that do not form *intra*molecular base pairs but do form *inter*molecular hybrids. Furthermore, the only teaching in Kutyavin et al. of any enzymatic synthesis method introduces only one selective nucleotide, and not its partner. The product of this enzymatic reaction, therefore, is not an unstructured nucleic acid that forms *inter*molecular, but not *intra*molecular base pair interactions. Kutyavin et al. provides no teaching or suggestion of provision of an appropriate collection of nucleotides selected to achieve production of a nucleic acid strand that forms *inter*molecular but not *intra*molecular base pair interactions.

Woo et al. (*Nucleic Acids Research* (1996) 24:2470-2475) describe selective hybridization properties of modified nucleotides that are similar to those described by Kutyavin et al. except that the modifications are within the G and C nucleotides. Woo et al. show that pairs of synthetic complementary oligonucleotides that include A, T, and the modified nucleotides inosine (I) and 3-(2-deoxy-β-D-ribofuranosyl)pyrrolo-[2,3-d]-pyrimidine-2-(3H)-one (P), are unable to form stable hybrids due to the destabilization between I and P nucleotides (I≠P). However, these modified oligonucleotides are able to form stable hybrids with complementary oligonucleotides that contain the four natural nucleotides A, T, G, and C due to selective hybridization properties A=T; T=A; I=C; P=G. Like Kutyavin et al., Woo et al. are limited to pairs of complementary oligonucleotides that are generated by chemical synthesis

methods, such as phosphoramidite synthesis chemistry. Additionally, Woo et al. provide no teaching or suggestion of nucleic acids with complementary sequence elements that do not form *intra*molecular base pairs but do form *inter*molecular hybrids.

Kutyavin et al. II. (U.S. Patent No. 5,912,340; the '340 patent) discloses the design, properties, synthesis, and composition of matter for a pair of synthetic oligonucleotides wherein each member of the pair is complimentary to a target duplex nucleic acid sequence. The pair of oligonucleotides is modified such that they do not form stable hybrids with one another. Like the base pairing combinations of Kutyavin et al. and Woo et al., the '340 patent describes various types of mutually exclusive base-pairs that lead to the inability of certain pairs of synthetic oligonucleotides to hybridize, including D≠sT and I≠P. The '340 patent, whose focus is on generating short probes for therapeutic and diagnostic purposes, provides no teaching or suggestion of nucleic acids with complementary sequence elements that do not form *intra*molecular base pairs but do form *inter*molecular hybrids, nor does it provide any teaching or suggestion of enzymatic synthesis methods for nucleic acids.

Incorporation of modified polynucleotides by DNA polymerases

There is a considerable body of literature, which demonstrates that both ribo and 2'-deoxynucleotide triphosphates can be incorporated into polynucleotides using template-dependent RNA and DNA polymerases. The purposes for introducing various modified nucleotides into polynucleotides are many, some of which are worth discussing here. These include, among others, a) reducing "compression" artifacts in polyacrylamide gels used for sequence analyses, b) stabilizing target/probe duplex hybrids, c) normalizing target/probe duplex stabilities in an GC/AT content independent manner, d) introducing defined mutations into polynucleotides, e) investigating the structural mechanisms of molecular recognition between two nucleic acids and/or a nucleic acid and a defined ligand, and f) expanding the natural four nucleotide, two base-pair scheme into one possessing six or more nucleotides and three or more specific base-pairing schemes.

Below is a brief review of selected examples of each of the above subcategories of art. However, please note that there are many examples that fall into one or more of the above categories, none of which teach or suggest the presently claimed invention. By contrast, the existence of this body of art establish that those of ordinary skill, once informed of the inventive

demonstration of enzymatic synthesis of unstructured nucleic acids by selecting appropriately designed collections of nucleotides, would readily be able to identify alternative or additional nucleotide sets equally useful in the practice of the claimed invention.

a) *Reducing "compression" artifacts in polyacrylamide gels used for sequence analyses.*

McDougall et al. (*Nucleosides, Nucleotides, and Nucleic Acids* (2001) 20:501-506) summarize the effects of DNA polymerase-mediated incorporation of various analogues of 2'-deoxyguanosine triphosphate (dGTP) into polynucleotides on the compression artifacts in sequencing polyacrylamide gel electrophoresis (PAGE). Compression artifacts are believed to be caused by local secondary structures forming within migrating nucleic acid fragments. Specifically, they studied 24 analogues primarily derived from inosine triphosphate and 7-deaza-2'-deoxyguanosine triphosphate. Four analogues were efficiently and specifically incorporated by the polymerase and reduced band compression in PAGE. McDougall et al. therefore demonstrate that one of ordinary skill in the art could, without undue experimentation, identify modified nucleotides that can be specifically and efficiently incorporated into polynucleotides. The reference, however, has no teaching or suggestion of unstructured nucleic acids or of methods of preparing them enzymatically, as is recited in the present claims.

b) *Stabilizing target/probe duplex hybrids.*

Hacia et al. (*Nucleic Acids Research* (1998)26:4975-4982) describe the effect of incorporating duplex stabilizing nucleotides into an RNA target molecule on its ability to hybridize with DNA probes in a high-density microarray format. Hacia et al. show that while 2-aminoadenosine, 5-methyluridine and 5-(1-propynyl)uridine can be efficiently incorporated into the RNA target molecule using both T7 and T3 RNA polymerase, the 2-aminoadenosine, 5-methyluridine is not as efficiently incorporated. Nevertheless, Hacia et al. show that each of these modified uridines, when incorporated into the RNA target molecule independently, can enhance the hybridization stability between the modified target and array probes, particularly in A/T rich regions. This reference does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by an RNA or DNA polymerase.

Nguyen et al. (*BMC Biotechnology* (2002) 2:14-29) demonstrate that 2-aminoadenosine, 5-methyluridine, and 5-methylcytidien triphosphates can be incorporated into RNA using T7 RNA polymerase at a sufficient efficiency to perform hybridization on high-density micorarrays. As with Hacia et al. (*supra*), Nguyen et al. (2002) utilize duplex stabilizing nucleotides to increase hybridization efficiency. This reference does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by an RNA or DNA polymerase.

c) *Normalizing target/probe duplex stabilities in a GC/AT content independent manner.*

Nguyen et al. (*Nucleic Acids Research* (1997) 25:3059-3065) showed that in chemically synthesized oligonucleotides, dC^{4Et} forms a specific base-pair with guanosine having a stability in the affinity range of a natural A=T base pair. Later, Nguyen et al. (*Nucleic Acids Research* (1998) 26:4249-4258) showed that the triphosphate form of dC^{4Et} could be specifically incorporated into longer polynucleotides using Klenow DNA polymerase or Taq DNA polymerase. The relative efficiencies of this incorporation are 9 and 6 times lower than that of the natural dCTP, respectively. The focus of this reference is on generating "normalized" stabilities in polynucleotides containing dC^{4Et}. This reference does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by an DNA polymerase.

d) *Introducing defined mutations into polynucleotides.*

Zaccolo et al. (*J. Mol. Biol.* (1996) 255:589-603) disclose that certain nucleotide triphosphate forms of modified nucleotides (e.g., 6-(2-deoxy-b-D-ribofuranosyl)-3,4-dihydro-8H-pyrimido-[4,5-C] [1,2]oxazin-7-one (dP)(and 8-oxo-2'-deoxyguanosine (8-oxodG)) can be incorporated by Taq DNA polymerase. However, this results in misincorporations in the form of A to C and T to G transition mutations. This reference does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base

pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by DNA polymerase.

Moriyama et al. (*Nucleic Acids Res.* (1998) 26:2105-2111) have shown that the triphosphate form of the degenerate modified nucleotide 6-(B-D-ribofuranosyl)-3,4-dihydro-8H-pyrimido[4,5-c]-[1,2]oxazin-7-one (P) can be efficiently incorporated opposite both G and A in a template nucleic acid by T3, T7 and SP6 phage RNA polymerases. In addition, Moriyama et al. show that the substitution of all U nucleotides in the HIV TAR RNA with P results in an RNA having near wild type characteristics with respect to melting temperature and Tat peptide binding. This modification has little or no effect on nucleotide structure and does not involve selected sets of nucleotides. Thus, Moriyama et al. does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by phase RNA polymerases.

e) *Investigating the structural mechanisms of molecular recognition between two nucleic acids and/or a nucleic acid and a defined ligand.*

Bailly and Waring (Bailly, C., and Waring, M.J., *Nucleic Acids Res.* (1998) 26:4309-4214; Bailly, C., and Waring, M.J. *J. Am. Chem. Soc.* (1995) 117;7311-7316; Bailly, C., and Waring, M.J., *Nucleic Acids Res.* (1995) 23:885-892), describe studies where the modified nucleotide 2-amino-2'-deoxyadenosine was incorporated into DNA, using a DNA polymerase, to assess its effect on the molecular recognition of DNA by ligands such as the antibiotics bleomycin and calicheamicin. The goal of these studies was to alter the functional groups within the minor groove of the DNA double helix, without significantly altering the geometry of the DNA double helix, so that specific interactions between the ligand and the DNA could be elucidated. Because the base pairing between 2-amino-2'-deoxyadenosine and thymidine is essentially isomorphic with an A=T base pair in the major groove and isomorphic with a G=C base pair in the minor groove, specific groove binding modes of the drug were distinguished. This reference does not teach or suggest the synthesis of nucleic acid molecules capable of *inter*molecular base pairing, but not *intra*molecular base pairing, as recited in the present claims, but does provide an example of how one skilled in the art can select modified nucleotides that are suitable for incorporation by DNA polymerase.

Ortoleva-Donnelly et al. (*Biochemistry* (19980 37:12933-12942) provide an example of how a polynucleotide having an incorporated modified nucleotide can be used to probe nucleic acid structure. This reference is another example of how one of ordinary skill in the art can tailor a modified nucleotide, such as 5'-O-(1-thio)-N2-methylguanosine, for incorporation into a polynucleotide using an RNA polymerase. However, this reference does not teach or suggest UNAs or methods of making them, as recited in the present claims. For example, the 5'-O-(1-thio)-N2-methylguanosine nucleotide, as utilized by Ortoleva-Donnelly et al., is designed to maintain Watson-Crick base-pairing potential with C (G=C) and not disrupt intramolecular secondary structure. In addition, Ortoleva-Donnelly et al. do not disclose the inclusion of a compensatory nucleotide in a second nucleic acid molecule that would restore hybrid formation.

f) *Expanding the natural four nucleotide, two base-pair scheme into one possessing six or more nucleotides and three or more specific base-pairing schemes.*

Various novel base pairing schemes that are mutually exclusive from the natural A=T and G=C schemes were developed (Switzer et al., *Biochemistry* (1993) 32:10489-10496; Horlacher et al., *Proc. Natl. Acad. Sci. USA* (1995) 92:63239-6333; Lutz et al., *Nucleic Acids Res.* (1996) 24:1308-1313). These base pairing schemes involve the non-natural nucleotides isoG and isoC or the nucleotides xanthosine and 2, 4,-diaminopyrimidine. The nucleotide triphosphate form of one member of each of these pairs can be incorporated opposite the other member in a DNA template using a DNA polymerase.

Another novel base pairing scheme has been developed that utilizes complementary hydrophobic interactions rather than hydrogen-bonding interactions to provide base pairing stability and specificity (Wu et al., *J. Am Chem. Soc* (2000) 122:7621-7632; McMinn et al. *J. Am. Chem. Soc.* (1999) 121:11585-11586). A number of DNA polymerases are able to incorporate the nucleotide triphosphate corresponding to one member of the hydrophobic pair opposite the other member of the hydrophobic pair in the DNA template.

Analogous base pairing schemes for RNA that utilize hydrogen bonding to impart specificity have also been developed. T7 RNA polymerase can specifically incorporate a 5-methylpyridin-2-1 triphosphate opposite the modified nucleotide 2-amino-6-(N,N-dimethylamino)purine in the DNA template (Ohtsuki et al., *Proc. Natl. Acad. Sci. USA* (2001) 98:4922-4925).

The motivation behind each of the above studies is to expand the natural two base pairing scheme three or more base pairing schemes, while *not* altering the structural stability or fundamental hybridization properties of the polynucleotides. The above base pairing schemes are designed to be specific and orthogonal to one another and therefore do not possess the mutually exclusive base pairing properties that define the nucleotides that comprise UNAs. These references do, however, provide an example of the diversity of nucleotides that can be specifically incorporated by a DNA polymerase. In view of the above searches and analyses, Applicant respectfully requests that the searching strategy of the Examiner be reconsidered so that it more accurately reflect the invention claimed.

Applicant respectfully disagrees with the finality of the Restriction based on the above facts.

Objection to the Drawings

The Examiner states that correction of the drawings is required. Formal drawings are submitted herewith. Withdrawal of this objection is respectfully requested.

Objection to the Claims

Claim 20 was objected to because line 2 states the following typographical error: "providing a at least one...". Claim 20 has been amended. Applicant apologizes for this oversight and requests withdrawal of the objection.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-8 and 19-24 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states that the claims are drawn to a broad scope of methods of synthesizing any type of unstructured nucleic acid molecule by providing any type of nucleic acid template (DNA, RNA, etc.), providing any type of nucleotide precursors (DNA, RNA, etc.) for synthesis of the unstructured nucleic acid with the elected T7 polymerase. In support of this statement, the Examiner points to Irtoleva-Donnelly et al. (Biochemistry, 1998, Vol. 37, pp.12933-12942) and states that "T7 RNA polymerase is not

useful for the incorporation of some modified nucleobases into ribozyme RNAs" (see page 6 of the Office Action). The Examiner concludes that one skilled in the art would not have expected that any known nucleotide analogue would have been acceptable for use in the claimed methods steps since the genus of all such possible nucleotide analogs does not provide one skilled in the art with a representative number of species of such analogues known to function specifically with T7 RNA polymerase. Applicant disagrees.

The Examiner requires that every conceivable embodiment falling within the claims perform successfully. If this were the standard, generic claims would never be allowable in any instance in which an Examiner can imagine or point to a single inoperative embodiment. This is not the standard the law requires. For example, in *Application of Angstadt,* 537 F2.d 498, 190 U.S. P.Q. 218 (C.C.P.A. 1976), the Court, in holding that a claimed invention was enabled though the claim admittedly included inoperative embodiments, stated that "the evidence as a whole, including the inoperative as well as operative example, negates the PTO position that persons of ordinary skill in this art, given its unpredictability, must engage in undue experimentation to determine which complexes work." The present specification, as filed, meets this requirement. The specification teaches general rules for choosing nucleotide combinations for synthesizing unstructured nucleic acids (page 15, line 19 to page 17, line 3). The specification further provides detailed examples of nucleotide combinations that can be used in the present invention to generate unstructured UNAs (see page 21, line 22 to page 29, line 3 and Examples 1-5).

The Examiner points to Irtoleva-Donnelly as a reference that teaches a base that is not incorporated by T7 polymerase. If a reference, such as Irtoleva-Donnelly et al. taught that T7 RNA polymerase is *not* useful with certain modified nucleotides, such as m2GalphaS, one skilled in the art would avoid using such nucleotides with T7 RNA polymerase. Instead, the skilled artisan would choose, based on what is known in the art, nucleotides that are compatible with T7 RNA polymerase, which would generate unstructured nucleic acids based on the teachings of the specification. The Examiner further acknowledges that a skilled artisan, having knowledge of the desirability of creating "unstructured" nucleic acids, as defined in the specification, would be able to choose from among the universe of nucleotides, those that would work. Specifically, the Examiner points out that Nguyen and Southern (who had possession of the inventive concept) "specifically state that *one skilled in the art uses those modified*

nucleosides known to be useful with certain classes of polymerase" (see page 3 of the Office Action). Indeed, the skilled artisan would look to what is known in the art to select the base compositions of the unstructured nucleic acids of the invention. Before the invention, such base compositions were unknown.

The Examiner states that "the claims are drawn to a broad scope of methods of synthesizing *any* type of unstructured nucleic acid molecule by providing *any* type of nucleic acid template (DNA, RNA, etc.), providing *any* type of nucleotide precursors (DNA, RNA, etc.) for synthesis of the unstructured nucleic acid with the elected T7 polymerase" (see page 6 of the Office Action). Applicant asserts that the claims do not recite just "any" nucleotide, but provide specific functional limitations that can be applied to select the nucleotide, which can be used by those skilled in the art. For example, claim 1 recites

> "nucleotide precursors sufficient to synthesize a nucleic acid strand complementary to at least a portion of the template nucleic acid strand, which portion includes the first and second template sequence elements, the collection including first and second complementary nucleotides, wherein the first and second complementary nucleotides have a reduced ability to form an intramolecular base pair but can form an intermolecular base pair."

Any person skilled in the art could select nucleotide compositions based on these criteria.

Applicant provides one skilled in the art with sufficient guidance to select such nucleotides. For example, the specification states that "any structural modifications to a nucleotide that do not inhibit the ability of an enzyme to incorporate the nucleotide analogue may be used in the present invention if the modifications do not result in a violation of the base pairing rules set forth in the present invention" (page 21, lines 22-25). Those rules are described as follows:

> "UNAs are produced such that sequence elements in the UNA have a reduced ability to hybridize to substantially complementary sequence elements within the same UNA

polynucleotide molecule. Complementary nucleotides for producing UNAs are selected such that a first nucleotide base is not capable of forming a stable base pair with a nucleotide complement. The two complementary nucleotides may have one naturally-occurring base and one base analog or may have two base analogs. The complementary nucleotides that are unable to form a stable base pair are used to produce UNA with reduce levels of intramolecular base pairing by reducing hybridization between sequence elements within the UNA that are substantially complementary. Complementary nucleotides that are unable to form stable pairs may also be used in sequences of the UNA that do not have substantially self-complementary sequences within the same UNA polynucleotide molecule.

In addition, it is preferable that the complementary nucleotides in a UNA that are unable to form stable base pairs, are capable of forming stable base pairs with at least one nucleotide complement present in a second polynucleotide molecule. Preferably, the second polynucleotide molecule contains sequence elements substantially complementary to sequence elements in the UNA to allow hybridization of part of all of the second polynucleotide to the UNA. Complementary sequence elements of the second polynucleotide may contain naturally-occurring bases or base analogs."

The above description, in combination with the more specific examples provided in the specification (see page 15, line 19 to page 17, line 3; page 21, line 22 to page 29, line 3 and Examples 1-5), is sufficient to guide any person skilled in the art to synthesize unstructured nucleic acids according to the invention. Thus, Applicant asserts that the specification provides a written description sufficient to meet the enablement standard for the claims.

It is not the particular nucleotide base or polymerase combination that is the inventive aspect of the claims. It is the recognition that nucleotide compositions may be selected for a

nucleic acid molecule, which have a reduced ability to form intramolecular base pairs, while maintaining the ability to form intermolecular base pairs. Such nucleic acids have reduced secondary structure, which is a valuable characteristic for many applications (see pages 29-32 of the application as filed). Based on the above facts, the present invention is described in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant requests withdrawal of this rejection.

Conclusion

Applicant respectfully requests entrance of the above Amendment and consideration of the above Remarks. Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 50-1078.

Respectfully submitted,

Dated: July 1, 2003

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Kathy Hart Gogan